



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2501245 A1 2004/04/22

(21) **2 501 245**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2003/10/09

(87) Date publication PCT/PCT Publication Date: 2004/04/22

(85) Entrée phase nationale/National Entry: 2005/04/04

(86) N° demande PCT/PCT Application No.: EP 2003/011205

(87) N° publication PCT/PCT Publication No.: 2004/032903

(30) Priorité/Priority: 2002/10/09 (102 47 037.5) DE

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 9/16, A61K 31/513

(71) Demandeur/Applicant:
ABBOTT GMBH & CO. KG, DE

(72) Inventeurs/Inventors:
ROSENBERG, JOERG, DE;
BERNDL, GUNTHER, DE;
MAEGERLEIN, MARKUS, DE

(74) Agent: ROBIC

(54) Titre : PRODUCTION DE FORMES GALENIQUES SOLIDES AU MOYEN D'UN EXCIPIENT NON
THERMOPLASTIQUE RETICULE

(54) Title: METHOD FOR PRODUCING SOLID GALENIC FORMULATIONS USING A CROSSLINKED NON-
THERMOPLASTIC CARRIER

(57) Abrégé/Abstract:

The invention concerns a method for producing solid galenic formulations which consists in: forming a processable paste comprising a) 50 to 99.4 wt. % of at least one non-thermoplastic carrier, b) 0.5 to 30 wt. % of at least an adjuvant selected among thermoplastic polymers, lipids, sugar alcohols and solubilizing agents, c) 0.1 to 49.5 wt. % of at least one active principle, at a temperature not less than the softening temperature of the adjuvant but rising to at least 70 °C; then in cooling the resulting paste. Said solid galenic formulations quickly disintegrate in an aqueous medium.



(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG(19) Weltorganisation für geistiges Eigentum
Internationales Büro(43) Internationales Veröffentlichungsdatum
22. April 2004 (22.04.2004)

PCT

(10) Internationale Veröffentlichungsnummer

WO 2004/032903 A3

(51) Internationale Patentklassifikation⁷: A61K 9/16, 31/513

(21) Internationales Aktenzeichen: PCT/EP2003/011205

(22) Internationales Anmeldedatum:
9. Oktober 2003 (09.10.2003)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
102 47 037.5 9. Oktober 2002 (09.10.2002) DE

(71) Anmelder (für alle Bestimmungsstaaten mit Ausnahme von US): ABBOTT GMBH & CO. KG [DE/DE]; Max-Planck-Ring 2, 65205 Wiesbaden (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder (nur für US): ROSENBERG, Jörg [DE/DE]; Bruchstr. 29, 67158 Ellerstadt (DE). BERNDL, Gunther [DE/DE]; Am Dörrling 7, 67273 Herxheim (DE). MÄGERLEIN, Markus [DE/DE]; Eichendorffstrasse 8, 68167 Mannheim (DE).

(74) Anwälte: KINZEBACH, Werner usw.; Reistötter, Kinzebach & Partner (GbR), Sternwartstrasse 4, 81679 München (DE).

(81) Bestimmungsstaaten (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten (regional): ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

— mit internationalem Recherchenbericht

(88) Veröffentlichungsdatum des internationalen
Recherchenberichts: 11. November 2004

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: METHOD FOR PRODUCING SOLID GALENIC FORMULATIONS USING A CROSSLINKED NON-THERMOPLASTIC CARRIER

(54) Bezeichnung: HERSTELLUNG VON FESTEN DOSIERUNGSFORMEN UNTER VERWENDUNG EINES VERNETZTEN NICHT-THERMOPLASTISCHEN TRÄGERS

(57) Abstract: The invention concerns a method for producing solid galenic formulations which consists in: forming a processable paste comprising a) 50 to 99.4 wt. % of at least one non-thermoplastic carrier, b) 0.5 to 30 wt. % of at least an adjuvant selected among thermoplastic polymers, lipids, sugar alcohols and solubilizing agents, c) 0.1 to 49.5 wt. % of at least one active principle, at a temperature not less than the softening temperature of the adjuvant but rising to at least 70 °C; then in cooling the resulting paste. Said solid galenic formulations quickly disintegrate in an aqueous medium.

(57) Zusammenfassung: Beschrieben wird ein Verfahren zur Herstellung fester Dosierungsformen, bei dem man eine formbare Masse, die a) 50 bis 99,4 Gew.-% wenigstens eines nicht-thermoplastischen Trägers, b) 0,5 bis 30 Gew.-% wenigstens eines unter thermoplastischen Polymeren, Lipiden, Zuckeralkoholen, Zuckeralkoholderivaten und Solubilisatoren ausgewählten Adjuvans und c) 0,1 bis 49,5 Gew.-% wenigstens eines Wirkstoffs umfasst, bei einer Temperatur bei 10 oder oberhalb des Erweichungspunkts des Adjuvans, mindestens jedoch 70 °C, bildet und anschließend abkühlt. Die Dosierungsformen zerfallen in wässriger Umgebung rasch.

WO 2004/032903 A3

**METHOD FOR PRODUCING SOLID GALENIC FORMULATIONS USING A
CROSSLINKED NON-THERMOPLASTIC CARRIER**

Description

The present invention relates to a process for producing fast-release solid dosage forms.

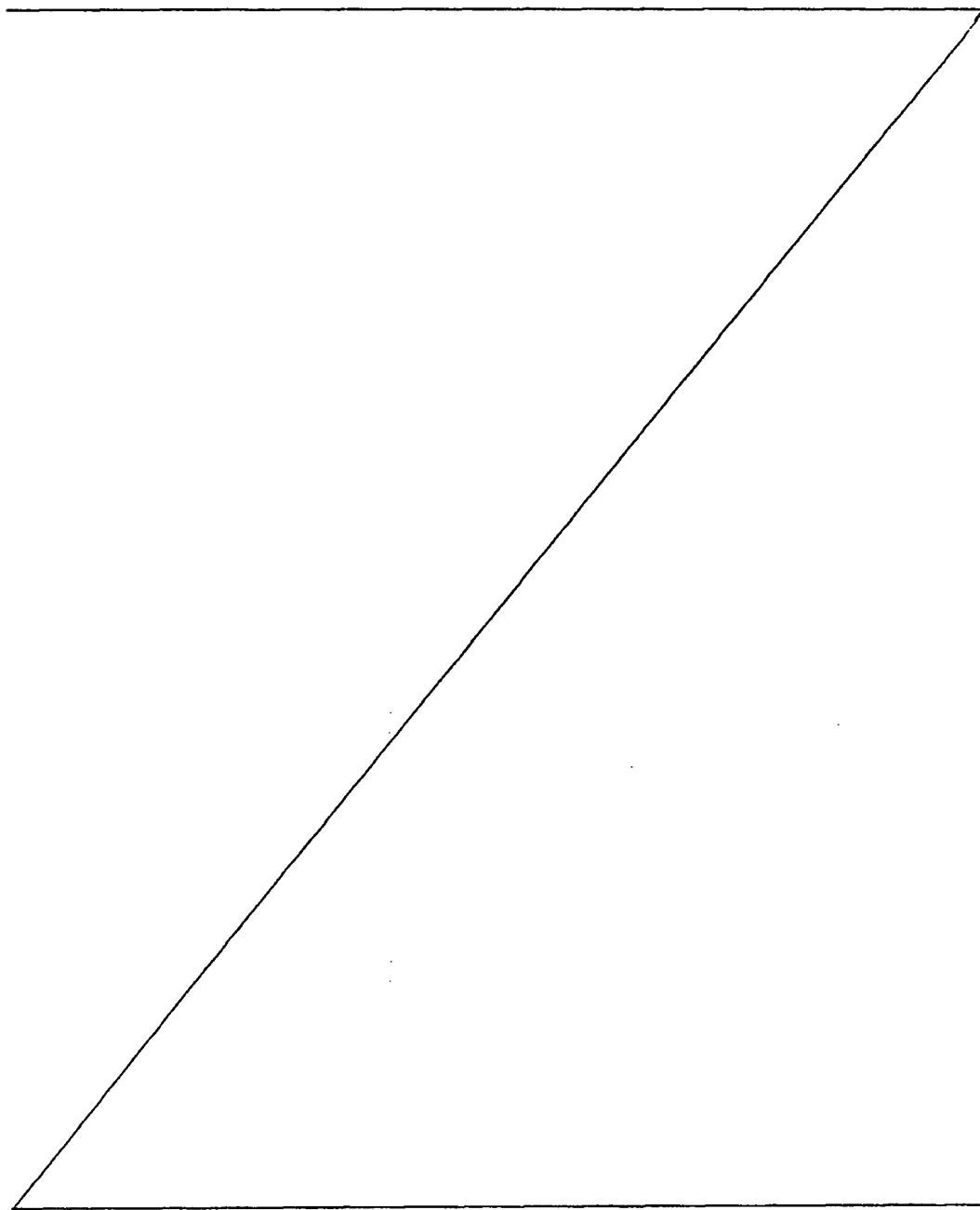
10 The production of solid dosage forms by melt extrusion, i.e. a process in which a melt of a polymeric binder and of an active ingredient is extruded, and the extrudate is shaped to the desired drug form, is known, see, for example, EP-A 240 904, EP-A 240 906, EP-A 337 256 and EP-A 358 105. This process permits the preparation of slightly soluble active ingredients in the form of solid solutions. The active ingredient is present in the solid solutions in amorphous form and can therefore be absorbed more easily than the crystalline active ingredient. However, the dissolution of the dosage form and the release of the active
20 ingredient takes place only at the surface of the dosage form. In many cases, however, rapid disintegration of the dosage form is desired.

EP-B 0078430 discloses a process for producing fast-release pharmaceutical preparations comprising dihydropyridine, polyvinylpyrrolidone and insoluble carriers such as crosslinked polyvinylpyrrolidone, where the active ingredient and the polyvinylpyrrolidone are dissolved in an organic solvent, and the solution is granulated with the carrier. This process cannot, however, be directly applied to other
30 slightly soluble active ingredients because a suitable physiologically tolerated solvent does not exist for all active ingredients and/or complete removal of the

1a

solvent is impossible or possible only in a troublesome manner.

GB 2 153 676 proposes the loading of water-insoluble



M/42135-PCT

- 2 -

polymers such as crosslinked polyvinylpyrrolidone with an active ingredient by mixing the polymer with the active ingredient and heating to the melting point of the active ingredient. This procedure has the disadvantage that many active ingredients cannot be melted without decomposition.

EP-A 0 446 753 discloses the loading of crosslinked polymers with an active ingredient by treating the polymer with a solution of the active ingredient, or grinding the polymer and the active ingredient with high energy input. The process has the disadvantage that it cannot be carried out continuously.

DE-A 44 13 350 describes slow-release matrix pellets consisting of an active ingredient, 5 to 50% by weight of a water-insoluble polymer such as ethylcellulose, 5 to 45% by weight of a lipophilic component, 3 to 40% by weight of a gel former such as hydroxypropylcellulose, and where appropriate formulation aids. The slow-release matrix pellets can be produced by melt extrusion.

It is an object of the invention to indicate a universally applicable process which allows dosage forms with rapid release in particular of slightly soluble active ingredients to be produced without the need to use organic solvents or to melt the active ingredient.

30

The present invention therefore relates to a process for producing solid dosage forms, in which a moldable composition which comprises

a) 50 to 99.4% by weight, preferably 60 to 80% by weight, of at least one crosslinked nonthermo-plastic carrier,

M/42135-PCT

- 3 -

- b) 0.5 to 30% by weight, preferably 5 to 20% by weight, of at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and

5

- c) 0.1 to 49.5% by weight, preferably 5 to 25% by weight, of at least one active ingredient,

is formed at a temperature at or above the softening
10 point of the adjuvant, but at least 70°C, preferably 100 to 180°C, and subsequently cooled.

In preferred embodiments, the composition comprises

- 15 a) 50 to 90% by weight, preferably 60 to 80% by weight, of at least one crosslinked nonthermoplastic carrier,

- 20 b1) 5 to 30% by weight, preferably 7 to 15% by weight, of at least one thermoplastic polymer,

- b2) 0.5 to 20% by weight, preferably 5 to 10% by weight, of at least one solubilizer,

- 25 c) 0.1 to 45.5% by weight, preferably 5 to 25% by weight, of at least one active ingredient.

The crosslinked nonthermoplastic carrier acts as disintegrant which brings about rapid disintegration of
30 the dosage form in an aqueous environment such as gastric juice. It is surprisingly possible to produce the dosage forms, which comprise a predominant proportion of a crosslinked nonthermoplastic carrier, in the absence of solvents through a process similar to
35 melt extrusion if particular adjuvants are additionally used. "Adjuvant" or "adjuvants" mean excipients which remain in the dosage form and are not merely added during production and are removed again in a later

M/42135-PCT

- 4 -

processing step.

Dosage forms mean all forms suitable for use as medicaments, in particular for oral administration, 5 plant-treatment compositions, animal feeds and dietary supplements. They include for example tablets of any shape, pellets or granules.

The crosslinked nonthermoplastic carrier is a natural, 10 semisynthetic or fully synthetic polymer which is crosslinked to a degree of crosslinking such that it has no thermoplastic properties. It is usually insoluble in water but swellable in water. The nonthermoplastic carrier is preferably selected from 15 crosslinked polyvinylpyrrolidone and crosslinked sodium carboxymethylcellulose. Crosslinked polyvinylpyrrolidone is most preferred. Suitable products are described for example in the US Pharmacopeia (USP NF).

20 Besides the active ingredient and the crosslinked nonthermoplastic carrier, there is also employed in the process of the invention at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers.

25

Examples of suitable thermoplastic polymers are polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone and vinyl acetate or vinyl propionate, copolymers of vinyl acetate and crotonic acid, 30 partially hydrolyzed polyvinyl acetate, polyvinyl alcohol, polyhydroxyalkylacrylates, polyhydroxyalkylmethacrylates, polyacrylates and polymethacrylates (Eudragit types), copolymers of methyl methacrylate and acrylic acid, polyethylene glycols, alkylcelluloses, 35 especially methylcellulose and ethylcellulose, hydroxyalkylcelluloses, especially hydroxypropylcellulose (HPC), hydroxyalkylalkylcelluloses, especially hydroxypropylmethylcellulose (HPMC), cellulose esters such as

M/42135-PCT

- 5 -

cellulose phthalates, in particular cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and hydroxypropylmethylcellulose acetate succinate (HPMCAS). Of these, homo- or copolymers of vinyl-
5 pyrrolidone are particularly preferred, e.g. polyvinylpyrrolidone with Fikentscher K values of from 12 to 100, preferably 17 to 30, or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA), such as, for example, a
10 copolymer of 60% by weight VP and 40% by weight VA.

The thermoplastic polymers preferably have a softening temperature of from 60 to 180°C, in particular 70 to 130°C.

15

Suitable sugar alcohols are sorbitol, xylitol, mannitol, maltitol; a suitable sugar alcohol derivative is isomalt.

20 Suitable lipids are fatty acids such as stearic acid; fatty alcohols such as cetyl or stearyl alcohol; fats such as animal or vegetable fats; waxes such as carnauba wax; or mono- and/or diglycerides or phosphatides, especially lecithin. The fats preferably
25 have a melting point of at least 50°C. Triglycerides of C₁₂, C₁₄, C₁₆ and C₁₈ fatty acids are preferred.

Solubilizers mean pharmaceutically acceptable nonionic surface-active compounds. Suitable solubilizers include
30 sorbitan fatty acid esters, polyalkoxylated fatty acid esters such as, for example, polyalkoxylated glycerides, polyalkoxylated sorbitan fatty acid esters or fatty acid esters of polyalkylene glycols; or polyalkoxylated ethers of fatty alcohols. A fatty acid
35 chain in these compounds usually comprises 8 to 22 carbon atoms. The polyalkylene oxide blocks comprise on average from 4 to 50 alkylene oxide units, preferably ethylene oxide units, per molecule.

M/42135-PCT

- 6 -

Suitable sorbitan fatty acid esters are sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan tristearate, sorbitan trioleate, sorbitan monostearate,
5 sorbitan monolaurate or sorbitan monooleate.

Examples of suitable polyalkoxylated sorbitan fatty acid esters are polyoxyethylene(20)sorbitan monolaurate, polyoxyethylene(20)sorbitan monopalmitate,
10 polyoxyethylene(20)sorbitan monostearate, polyoxyethylene(20)sorbitan monooleate, polyoxyethylene(20)sorbitan tristearate, polyoxyethylene(20)sorbitan trioleate, polyoxyethylene(4)-sorbitan monostearate, polyoxyethylene(4)sorbitan
15 monolaurate or polyoxyethylene(4)sorbitan monooleate.

Suitable polyalkoxylated glycerides are obtained for example by alkoxylation of natural or hydrogenated glycerides or by transesterification of natural or
20 hydrogenated glycerides with polyalkylene glycols. Commercially available examples are polyoxyethylene glycerol ricinoleate 35, polyoxyethylene glycerol trihydroxystearate 40 (Cremophor® RH40, BASF AG) and polyalkoxylated glycerides obtainable under the
25 proprietary names Gelucire® and Labrafil® from Gattefosse, e.g. Gelucire® 44/14 (lauroyl macrogol 32 glycerides prepared by transesterification of hydrogenated palm kernel oil with PEG 1500), Gelucire® 50/13 (stearoyl macrogol 32 glycerides prepared by
30 transesterification of hydrogenated palm oil with PEG 1500) or Labrafil M1944 CS (oleoyl macrogol 6 glycerides prepared by transesterification of apricot kernel oil with PEG 300).

35 A suitable fatty acid ester of polyalkylene glycols is for example PEG 660 hydroxystearic acid (polyglycol ester of 12-hydroxystearic acid (70 mol%) with 30 mol% ethylene glycol).

M/42135-PCT

- 7 -

Suitable polyalkoxylated ethers of fatty alcohols are for example macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether

5 Besides these, it is possible additionally to use conventional pharmaceutical excipients, the total amount of which may be up to 20% by weight based on the dosage form. These include:

10 extenders or fillers such as lactose, cellulose, silicates or silica,

lubricants such as magnesium stearate and calcium stearate, sodium stearyl fumarate,

15

colorants such as azo dyes, organic or inorganic pigments or colorants of natural origin,

20 stabilizers such as antioxidants, light stabilizers, hydroperoxide destroyers, radical scavengers, stabilizers against microbial attack.

Active ingredients mean for the purposes of the invention all substances with a desired physiological
25 effect on the human or animal body or plants. They are in particular active pharmaceutical ingredients. The amount of active ingredient per dose unit may vary within wide limits. It is usually chosen so that it is sufficient to achieve the desired effect. Combinations
30 of active ingredients can also be employed. Active ingredients for the purposes of the invention are also vitamins and minerals. Vitamins include the vitamins of the A group, or the B group, by which are meant besides B₁, B₂, B₆ and B₁₂ and nicotinic acid and nicotinamide
35 also compounds having vitamin B properties such as, for example, adenine, choline, pantothenic acid, biotin, adenylic acid, folic acid, orotic acid, pangamic acid, carnitine, p-aminobenzoic acid, myo-inositol and lipoic

M/42135-PCT

- 8 -

acid, and vitamin C, vitamins of the D group, E group, F group, H group, I and J groups, K group and P group. Active ingredients for the purposes of the invention also include peptide therapeutics and proteins. Plant
 5 treatment agents include for example vinclozolin, epoxiconazole and quinmerac.

The process of the invention is suitable, for example, for processing the following active ingredients:

10

acebutolol, acetylcysteine, acetylsalicylic acid, acyclovir, albrazolan, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine,
 15 amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclomethasone, benserazide, benzalkonium hydrochloride, benzocaine, benzoic acid, betamethasone, bezafibrate, biotin, biperidene, bisoprolol, bromazepam, bromhexine, bromocriptine,
 20 budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefachlor, cefalexin, cefatroxil, cefazolin, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, celedilin, chloramphenicol,
 25 chlorhexidine, chlorpheniramine, chlortalidone, choline, cyclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clevulanic acid, clomibramine, clonazepam, clonidine, clotrimazole, codeine, cholestyramine, cromoglycic acid, cyanocobalamin, cyproterone, desogestrel,
 30 dexamethasone, dexpanthenol, dextromethorphan, dextro-propoxiphen, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, dihydroergotoxin, diltiazem, diphenhydramine, dipyridamole, dipyrone,
 35 disopyramide, domperidone, dopamine, doxycycline, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, Eucalyptus Globulus, famotidine, felodipine,

M/42135-PCT

- 9 -

fenofibrate, fenofibric acid, fenoterol, fentanyl,
flavin mononucleotide, fluconazole, flunarizine,
fluorouracil, fluoxetine, flurbiprofen, furosemide,
gallopamil, gemfibrozil, gentamicin, Ginkgo Biloba,
5 glibenclamide, glipizide, clozapine, Glycyrrhiza
glabra, griseofulvin, guaifenesin, haloperidol,
heparin, hyaluronic acid, hydrochlorothiazide, hydro-
codone, hydrocortisone, hydromorphone, ipratropium
hydroxide, ibuprofen, imipenem, indomethacin, insulin,
10 iohexol, iopamidol, isosorbide dinitrate, isosorbide
mononitrate, isotretinoin, ketotifen, ketoconazole,
ketoprofen, ketorolac, labatalon, lactulose, lecithin,
levocarnitine, levodopa, levoglutamide, levonorgestrel,
levothyroxine, lidocaine, lipase, lipramine,
15 lisinopril, loperamide, lorazepam, lovastatin, medroxy-
progesterone, menthol, methotrexate, methyldopa,
methylprednisolone, metoclopramide, metoprolol,
miconazole, midazolam, minocycline, minoxidil, miso-
prostol, morphine, multivitamin mixtures or
20 combinations and mineral salts, N-methylephedrine,
naftidrofuryl, naproxen, neomycin, nicardipine, nicer-
goline, nicotinamide, nicotine, nicotinic acid,
nifedipine, nimodipine, nitrazepam, nitrendipine, niza-
tidine, norethisterone, norfloxacin, norgestrel,
25 nortriptyline, nystatin, ofloxacin, omeprazole,
ondansetron, pancreatin, panthenol, pantothenic acid,
paracetamol, penicillin G, penicillin V, phenobarbital,
phenoxifylline, phenoxymethylpenicillin, phenylephrine,
phenylpropanolamine, phenytoin, piroxicam, polymyxin B,
30 povidone-iodine, pravastatin, prazepam, prazosin, pred-
nisolone, prednisone, promocriptine, propafenone,
propranolol, proxyphylline, pseudoephedrine,
pyridoxine, quinidine, ramipril, ranitidine, reserpine,
retinol, riboflavin, rifampicin, rutoside, saccharin,
35 salbutamol, salcatonin, salicylic acid, simvastatin,
somatropin, sotalol, spironolactone, sucralfate,
sulbactam, sulfamethoxazole, sulfasalazine, sulpiride,
tamoxifen, tegafur, teprenone, terazosin, terbutaline,

M/42135-PCT

- 10 -

terfenadine, tetracycline, theophylline, thiamine,
ticlopidine, timolol, tranexamic acid, tretinoin,
triamcinolone acetonide, triamteren, trimethoprim,
troxerutin, uracil, valproic acid, vancomycin,
5 verapamil, vitamin E, volinic acid, zidovudine.

The process is particularly suitable for active
ingredients having a solubility in water at 25°C of
less than 1 mg/ml. Such active ingredients are also
10 referred to according to USP XXII, page 8, as scarcely
soluble or practically insoluble.

The solid dosage forms are produced by producing, at an
elevated temperature, i.e. a temperature at or above
15 the softening point of the adjuvant, but at least 70°C,
a moldable cohesive composition of the components,
which is subsequently cooled, where appropriate after a
shaping step. The time for which the components are
exposed to the elevated temperature is preferably less
20 than 5 minutes, in particular less than 3 minutes, for
each of the components.

The mixing of the components and the formation of the
moldable composition can take place in various ways.
25 The mixing can take place before, during and/or after
the heating of one or all of the components of the
composition, although it is not expedient to heat the
crosslinked nonthermoplastic carrier in the absence of
the thermoplastic components of the composition. For
30 example, the components can first be mixed and then
heated to form the moldable composition. However, they
can also be mixed and heated simultaneously. The
moldable composition is frequently also homogenized in
order to obtain a highly dispersed distribution of the
35 active ingredient. In the case of sensitive active
ingredients, preferably the adjuvant(s) is (are)
initially melted in the presence of the
nonthermoplastic carrier and then the active ingredient

M/42135-PCT

- 11 -

is admixed.

The heating takes place in an apparatus usual for this purpose. Heatable extruders or kneaders are particularly suitable, such as mixer/kneader reactors (e.g. ORP, CRP, AP, DTB supplied by List or Reactotherm supplied by Krauss-Maffei or Ko-kneader supplied by Buss), trough mixers and internal mixers or rotor/stator systems (e.g. Dispax supplied by IKA). The residence time of the composition in the extruder is preferably less than 5 minutes, in particular less than 3 minutes.

Extruders which can be employed are single-screw machines, intermeshing screw machines or else multi-screw extruders, especially twin screw extruders, corotating or counter-rotating and, where appropriate, equipped with kneading disks. Twin screw extruders of the ZSK series from Werner & Pfleiderer are particularly preferred.

The charging of the extruder or kneader takes place continuously or batchwise according to the design thereof in a conventional way. Powdered components can be fed in freely, e.g. via a weigh feeder. Plastic compositions can be fed in directly from an extruder or fed in via a gear pump, which is particularly advantageous for high viscosities and high pressures. Liquid media can be metered in via a suitable pumping unit.

The resulting composition is doughy or pasty. It is usually subjected to a shaping. It is possible in this way to produce a large number of shapes, depending on the tool and mode of shaping. For example, on use of an extruder the extrudate can be shaped between a belt and a roll, between two belts or between two rolls, as described in EP-A-358 105, or by calendering in a

M/42135-PCT

- 12 -

calender with two molding rolls, see, for example, EP-A-240 904. Small-particle granules can be obtained for example by extrusion and hot or cold cut of the extrudate. The cooled compositions can then also be
5 ground to a powder and subsequently compressed to tablets in a conventional way. It is possible in this case also to use tableting aids such as colloidal silica, calcium hydrogen phosphate, lactose, microcrystalline cellulose, starch or magnesium
10 stearate.

The invention is illustrated in more detail by the following examples.

15 Examples

Example 1

A mixture of 20.83% by weight of active ingredient
20 (lopinavir), 68.17% by weight of crosslinked polyvinylpyrrolidone (Kollidon CL), 7.00% by weight of polyoxyethylene glycerol trihydroxystearate 40 (Cremophor® RH-40) and 1.00 by weight of Aerosil 200 was processed in a twin screw extruder (18 mm screw
25 diameter) at a material temperature of 120°C. The Cremophor® RH-40 had previously been mixed at room temperature with the powdered Kollidon CL with stirring or kneading to give free-flowing granules, to which the active ingredient and the Aerosil 200 were then
30 admixed. 1.5 kg/h of this mixture were then fed via a weigh feeder into the extruder. A hot moldable composition in the form of a white extrudate emerged from the extruder head and then hardened after cooling. The cooled extrudates (with a thickness of about 10 mm)
35 disintegrated in water within a few minutes.

Example 2

M/42135-PCT

- 13 -

Pieces of the extrudate obtained in example 1 were ground in a laboratory mill (from Retsch) and, after addition of 12% by weight of calcium hydrogen phosphate and 1% by weight of Aerosil 200 (colloidal silica),
5 compressed in an eccentric press (Fette E 1) to oblong tablets. The tablets showed a disintegration time of a few minutes in a disintegration test (complying with DAB) in 0.1 M hydrochloric acid at 37°C.

10 Example 3 (comparative example)

Example 1 was repeated but with use of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate (Kollidon VA-64) instead of Kollidon
15 CL. A translucent extrudate emerged from the extruder head and formed a hard brittle composition after cooling. The extrudates dissolved in water only after several hours.

20 Example 4 (comparative example)

Pieces of the extrudate obtained in example 3 were ground in analogy to example 2 and compressed with the stated excipients to oblong tablets. The disintegration
25 time of the tablets in a disintegration test (complying with DAB) was more than 3 hours.

Example 5

30 A mixture of 20.83% by weight of active ingredient (lopinavir), 61.17% by weight of crosslinked polyvinylpyrrolidone (Kollidon CL), 10.00% by weight of N-vinylpyrrolidone/vinyl acetate 60/40 copolymer (Kollidon VA-64), 7.00% by weight of Cremophor RH-40
35 and 1.00 by weight of Aerosil 200 was processed in analogy to example 1. A hot moldable composition in the form of a white extrudate emerged from the extruder head and hardened after cooling. The cooled extrudates

M/42135-PCT

- 14 -

disintegrated in water in a few minutes.

Example 6

5 A mixture of 20.83% by weight of active ingredient
(lopinavir), 51.17% by weight of crosslinked
polyvinylpyrrolidone (Kollidon CL), 20.00% by weight of
N-vinylpyrrolidone/vinyl acetate 60/40 copolymer
(Kollidon VA-64), 7.00% by weight of Cremophor RH-40
10 and 1.00 by weight of Aerosil 200 was processed in
analogy to example 1. A hot moldable composition in the
form of a yellowish white extrudate emerged from the
extruder head and hardened after cooling. The cooled
extrudates disintegrated in water in a few minutes.

15

Example 7

A mixture of 20.83% by weight of active ingredient
(lopinavir), 61.17% by weight of crosslinked
20 polyvinylpyrrolidone (Kollidon CL), 10.00% by weight of
N-vinylpyrrolidone/vinyl acetate 60/40 copolymer
(Kollidon VA-64), 7.00% by weight of sorbitan
monopalmitate (Span 40) and 1.00 by weight of Aerosil
200 was processed in analogy to example 1. A hot
25 moldable composition in the form of a yellowish white
extrudate emerged from the extruder head and hardened
after cooling. The cooled extrudates disintegrated in
water in a few minutes.

M/42135-PCT

- 15 -

We claim:

1. A process for producing solid dosage forms, in which a moldable composition which comprises

5

a) 50 to 99.4% by weight of at least one crosslinked nonthermoplastic carrier,

b) 0.5 to 30% by weight of at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and

c) 0.1 to 49.5% by weight of at least one active ingredient,

is formed at a temperature at or above the softening point of the adjuvant, but at least 70°C, and subsequently cooled.

20

2. The process according to claim 1, where the composition comprises

a) 50 to 90% by weight of at least one crosslinked nonthermoplastic carrier,

b1) 5 to 30% by weight of at least one thermoplastic polymer,

b2) 0.5 to 20% by weight of at least one solubilizer,

c) 0.1 to 45.5% by weight of at least one active ingredient.

35 3. The process according to claim 1 or 2, where the crosslinked nonthermoplastic carrier is selected from crosslinked polyvinylpyrrolidone and crosslinked sodium carboxymethylcellulose.

M/42135-PCT

- 16 -

4. The process according to any of the preceding claims, where the thermoplastic polymer is a homo- or copolymer of vinylpyrrolidone.

5

5. The process according to any of the preceding claims, where the sugar alcohol is selected from sorbitol, xylitol, mannitol, maltitol and the sugar alcohol derivative isomalt.

10

6. The process according to any of the preceding claims, where the lipid is selected from fatty acids, fatty alcohols, fats, waxes, mono- and diglycerides and phosphatides.

15

7. The process according to any of the preceding claims, where the solubilizer is selected from sorbitan fatty acid esters, polyalkoxylated fatty acid esters and polyalkoxylated ethers of fatty alcohols.

20

8. The process according to any of the preceding claims, where the active ingredient has a solubility in water at 25°C of less than 1 mg/ml.

25

9. The process according to any of the preceding claims, where the cooled composition is comminuted and compressed to the dosage form.